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1321433

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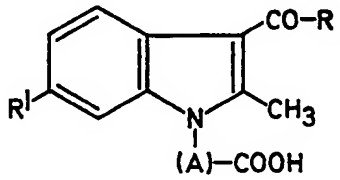
(19)

(54) 1,2,3,6-TETRASUBSTITUTED INDOLES

(17) We, ROUSSEL-UCLAF, a French Body Corporate of 35 Boulevard des Invalides, Paris 7e, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention, which is an improvement in or modification of the invention the subject of our patent No. 1,260,868 relates to 1,2,3,6-tetrasubstituted indoles having anti-inflammatory and analgesic activities.

Patent No. 1,260,868 describes and claims *inter alia* a class of indoles of general formula



(I)

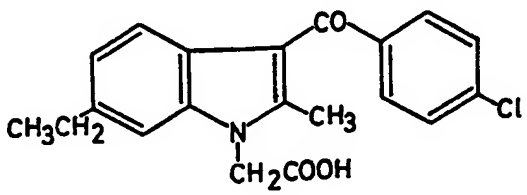
[wherein (A) represents a straight or branched chain alkylene group; R prepresents a cyclohexyl group or an aromatic group; R′ represents a (C_1—C_4) alkoxy group] the alkyl (C_1—C_4) esters thereof and the non-toxic base salts. Our said Patent further claims 1-carboxy-methyl-2-methyl-3-p-methoxy-benzoyl-6-chloro-indole and its methyl ester; 1-carboxymethyl-2-methyl-3-p-chloro-benzoyl-6-chloro-indole and its methyl ester; and dl-1-(α-carboxyethyl)-2-methyl-3-p-chlorobenzoyl-6-chloro-indole and its ethyl ester.

The above-mentioned compounds generally have valuable anti-inflammatory and/or analgesic action.

In further pursuance of our researches we have found that two new compounds structurally related to the compounds of our said Patent have particularly valuable pharmacological properties.

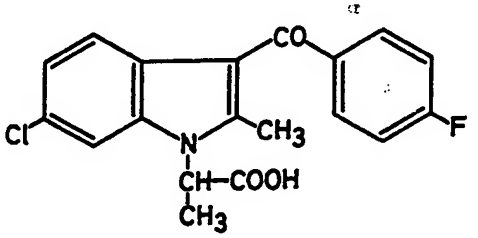
Thus, 1-carboxymethyl-2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole and its esters and salts, and 1-(1-carboxy-ethyl)-2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole have both been found to have especially good anti-inflammatory and analgesic activity. Moreover, both of the last-mentioned compounds have a considerably lower ulcerogenic action than various compounds of related structure such as indomethacine.

According to the present invention we provide compounds of formulae



(II)

and



(III)

and physiologically acceptable base salts and esters thereof. Such esters include for example C_{1-3} alkyl esters e.g. the methyl esters.

It will be apreciated that the compound of formula III may occur in the form of optical isomers, or racemic mixtures of such isomers, such isomers and mixtures thereof being included within the scope of the present invention.

The compound of formula III is useful for the treatment of muscular, articular, and nervous algias, dental pains, shingles, and migraine and in the complementary treatment of feverish and infectious conditions. The compound of formula II is useful in the treatment of ankylosing spondylarthritis, acute articular rheumatism, arthroses, slipped disc syndromes, lumbago, and shingles. The compound of formula II may also be used in the complementary treatment of feverish or infectious conditions.

According to a further feature of the present invention we provide pharmaceutical compositions comprising, as active ingredient, at least one compound according to the present invention, together with at least one pharmaceutical carrier or excipient.

The compositions of the invention may be presented in a form suitable for oral, transcutaneous, or rectal administration or in a form suitable for topical administration, e.g. to the skin or mucous membranes.

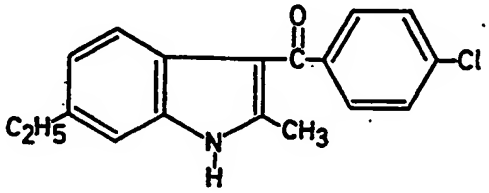
Thus, for example, compositions for oral administration may be solid or liquid and may take the form of granules, tablets, coated tablets, capsules, syrups, emulsions or drops, such compositions comprising carriers or excipients conventionally used in the pharmaceutical art.

For parenteral administration the compositions according to the invention may take the form of injectable solutions or suspensions, the carrier being a sterile, parenterally acceptable liquid such as sterile water, or a parenterally acceptable oil e.g. arachis oil, contained in ampoules. Compositions for rectal administration may take the form of suppositories, the carrier comprising a suppository base. Compositions for topical application may take the form of, for example, ointments, creams or powders.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tables, coated tablets, capsules, suppositories and ampoules are examples of suitable dosage unit forms. Each dosage unit preferably contains 25 to 250 mg of active ingredient.

The preferred daily dose for the adult of the compound of formula II or its esters or salts is generally 100 mg to 1 g depending upon the route of administration and also upon the nature of the therapeutic treatment and patient concerned. Similarly, the preferred daily dose for the adult of the compound of formula III is generally 25 mg to 2 g.

According to a still further feature of the present invention, we provide a process for the preparation of the compound of formula II (as defined above) and C_{1-8} alkyl esters thereof which comprises converting 2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole, of formula

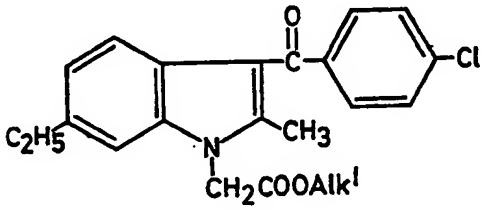


(IV)

to an alkali metal derivative thereof and reacting said derivative with an alkyl haloacetate of formula

$$Hal—CH_2—COOAlk'$$

(wherein Hal represents a chlorine, bromine or an iodine atom and Alk' represents an alkyl group containing 1—4 carbon atoms preferably a methyl or ethyl group) to produce a compound of formula



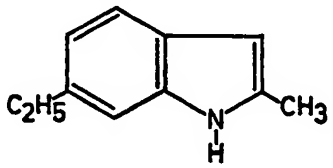
(V)

and if desired hydrolysing said last-mentioned compound to the corresponding free acid.

The conversion of the compound of formula IV to its alkali metal derivative may be carried out in conventional manner, by reaction with an alkali metal or alkali metal derivative such as an alkali metal amide, alkali metal hydride, an alkali metal alcoholate or a suitable alkali metal organometallic compound; generally it is convenient to form the sodium derivative of the compound of formula IV. The conversion is conveniently effected in an organic solvent, for example dimethyl formamide.

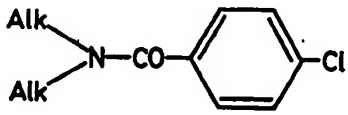
Hydrolysis of the esters of formula V may be carried out for example under basic conditions using for example potassium hydroxide or sodium hydroxide conveniently in an organic solvent such as an alkanol.

The compound of formula IV (as defined above) may be prepared for example, by acylating 2-methyl-6-ethylindole of formula



(VI)

with a compound of formula



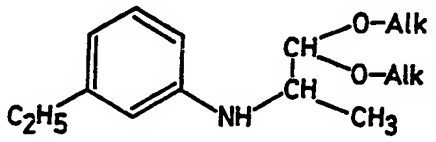
(VII)

(wherein the groups Alk, which may be the same or different, each represents an alkyl group). This reaction is effected under conditions suitable for effecting reactions of the Vilsmeier-Haack type, for example in the presence of phosphorus oxychloride, phosgene, or thionyl chloride. The resulting complex is hydrolysed under basic conditions to produce the compound of formula IV. The basic conditions in the last-mentioned reaction are preferably provided by a strong inorganic base such as sodium

or potassium hydroxide, and the hydrolysis is advantageously effected in the presence of an organic solvent such as alkanol.

The compound of formula VII may be prepared by reacting dialkylamine of formula $>N—H$ (wherein Alk is as hereinbefore defined) with *p*-chlorobenzoyl chloride.

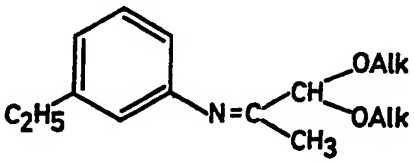
The compound of formula VI may be prepared for example by cyclising a compound of formula



(VIII)

(wherein Alk is as hereinbefore defined), with a cyclisation agent such as boron trifluoride to produce the compound of formula VII.

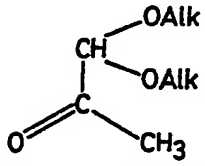
The said compound of formula VIII employed in the last-mentioned process may be prepared for example by reducing a compound of formula



(IX)

(wherein Alk is as hereinbefore defined) for example with an alkali metal borohydride such as sodium borohydride.

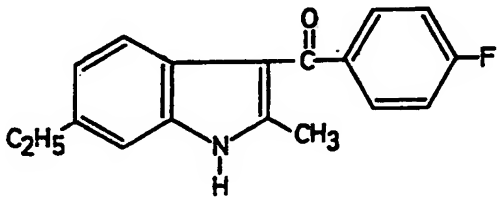
The said compound of formula IX may be prepared for example by reacting a compound of formula



(wherein Alk is as hereinbefore defined) with 3-ethylaniline.

The compound of formula II may, if desired, be esterified in conventional manner, for example by reaction with an appropriate alcohol advantageously in the presence of an acid catalyst. The compound of formula II may also, if desired, be converted into a salt thereof in conventional manner, for example, by reaction with an appropriate base.

According to a yet further feature of the present invention, we provide a process for the preparation of the compound of formula III (as defined above) and lower alkyl esters thereof which comprises converting 2-methyl-3-(*p*-fluorobenzoyl)-6-ethylindole, of formula

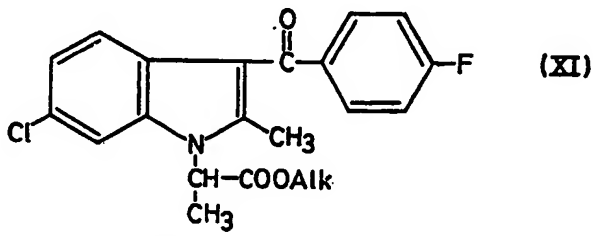


(X)

to an alkali metal derivative thereof and reacting said derivative with an alkyl 2-halopropionate of formula

$$CH_3—CHHal'—COOAlk$$

(wherein Hal' represents a halogen atom and Alk is as defined above) to produce a a compound of formula



(XI)

and if desired hydrolysing the last-mentioned compound to the corresponding free acid.

Thus the last-mentioned process may, if desired, be carried out in an analogous manner to that employed for the conversion of the compound of formula IV into the compound of formula II.

2-Methyl-3-(*p*-fluorobenzoyl)-6-chloroindole may be prepared for example, by acylating 2-methyl-6-chloroindole with N,N-dimethyl-*p*-fluorobenzamide. This reaction is effected under conditions suitable for effecting reactions of the Vilsmeier-Haack type for example in the presence of phosphorus oxychloride, thionyl chloride or phosgene, and subsequently hydrolysing the resulting complex under basic conditions to produce 2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole.

The preparation of 2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole according to the last-mentioned process may be carried out in an analogous manner to that employed for the preparation of the compound of formula VI from the compund of formula VII.

The compound of formula XI may be obtained in the form of a mixture of optical isomers thereof, in which case, it may, if desired, be resolved in conventional manner, e.g. by conversion into a salt thereof with an optically active base, followed by separation of the diastereoisomeric compounds so produced and then acidification of the appropriate diastereomer to produce the desired optical isomer of the compound of formula XI.

The following Examples illustrate the present invention while the Preparations illustrate the preparation of starting materials employed in the process of the invention.

Preparation: 2-methyl-6-ethylindole

Stage A: dimethyl acetal of 2-(3-ethylphenyl-imino)-propionaldehyde

A mixture of 15g 3-ethylaniline, [described by P. M. Kochergin, *Zhur. obshcher Khim.*, *27*, 3204, (1957) and *Chem. Abs.*, *52*, 8987, (1958)], 15g of the dimethyl acetal of pyruvaldehyde an iodide crystal, and 150ml toluene are refluxed for 24 hours, the water formed being distilled off by azeotropy and separated by decantation. The toluene is removed by distillation under reduced pressure, the residues from the two operations are combined, and 38g of this are redistilled. 30g of the dimethyl acetal of 2-(3-ethylphenyl-imino)-propionaldehyde are obtained in the form of a clear yellow liquid boiling at 163°C under 25mm mercury.

Analysis: $C_{13}H_{19}NO_2$ (221.29).

Calculated:	C%	70.55	H%	8.65	N%	6.33
Found:		70.5		8.6		6.4

Stage B: dimethyl acetal of 2-(3-ethylanilino)-propionaldehyde

A mixture of 25.5g of the dimethyl acetal of 2-(3-ethylphenyl-imino)-propionaldehyde, 800ml methanol, two drops of sodium hydroxide solution, and 13g sodium borohydride is boiled for two hours. The reaction mixture is poured into cold water, the mixture is extracted with ether, and the extract is dried over sodium sulphate and evaporated to dryness. 25 g of the residue are collected and redistilled under a pressure of 20 mm mercury. 18 g of the dimethyl acetal of 2-(3-ethylanilino)-propionaldehyde

are obtained in the form of a colourless liquid, soluble in conventional organic solvents, but insoluble in water, boiling, under 20 mm mercury, at 164°C (yield 70%).

Analysis: $C_{12}H_{21}NO_2$=223.31.

Calculated:	C%	69.92	H%	9.48	N%	6.27
Found:		70.2		9.6		6.1

Stage C: 2-methyl-6-ethylindole

17.2 g of the dimethyl acetal of 2-(3-ethylanilino)-propionaldehyde and 130 ml benzene are mixed, the internal temperature is brought to between 5°C and 10°C, and a stream of boron trifluoride is passed through for two hours with stirring, followed by a stream of nitrogen for 30 minutes. 50 ml water are added, stirring is continued for 15 minutes, and the mixture is separated by decantation. The benzene phase is washed with a 10% aqueous ammonia solution, dried over sodium sulphate, and evaporated to dryness. 15 g of the residue are collected and redistilled at a pressure of 1 mm mercury. 5g of crude product are obtained; this is recrystallized from petroleum ether. 3 g 2-methyl-6-ethylindole are obtained in the form of a solid product soluble in conventional organic solvents, but insoluble in water, melting at 68°C (yield 24%).

Analysis: $C_{11}H_{13}N$=159.22

Calculated:	C%	82.97	H%	8.23	N%	8.80
Found:		82.6		8.0		8.7

Example 1: 1-carboxymethyl-2-methyl-3-p-chlorobenzoyl-6-ethylindole.

Stage A: 2-methyl-3-(p-chlorobenzoyl)-6-ethylindole

6.2 g N,N-dimethyl-*p*-chlorobenzamide (compound described in the Beilstein dictionary, *9*, 341) are suspended in 2.5 ml phosphorus oxychloride; 2.8 g 2-methyl-6-ethylindole are added and the mixture is heated for 2 hours at 90°C. 50 ml of boiling ethanol are added, then the reaction mixture is poured into hot water with stirring. The solution is cooled and brought to pH=10 by the addition of sodium hydroxide solution, then stirred for an hour at 0°C and filtered; the precipitate is washed with ethanol, then ether. 3.5 g of crude 2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole are obtained, melting at 210°C; this is recrystallised from ethanol. Thus 3.2 g of the pure compound are obtained in the form of colourless crystals, soluble in dichloromethane, sparingly soluble in alcohols, but insoluble in water and ether; the melting point remains unchanged after recrystallization (yield 61%).

Analysis: $C_{18}H_{16}NClO$=297.78.

Calculated:	C%	72.63	H%	5.41	Cl%	11.80	N%	4.7
Found:		72.7		5.2		11.7		4.8

Stage B: 1-(methoxycarbonyl-methyl)-2-methyl-3-(p-chlorobenzoyl)-6-ethylindole

A solution of 3.2 g 2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole in 50 ml dimethylformamide is added to a suspension of 0.6 g of 50% sodium hydride in Vaseline oil (the word "Vaseline" is a registered Trade Mark) in 20 ml dimethylformamide; after contact for one hour when the hydrogen has been driven off, 1.7 g methyl chloracetate are added; the mixture is stirred for one night. The solvent is evaporated off and the residue is taken up in 100 ml water and filtered, washed with water and vacuum filtered. 5 g of the 1-(methoxycarbonyl-methyl)-2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole are collected and recrystallized from methanol. The compound is obtained in the form of yellow crystals, soluble in dichloromethane, sparingly soluble in alcohols, but insoluble in water, melting at 130°C (yield 63%).

Analysis: $C_{21}H_{20}NClO_3$=369.84.

Calculated:	C%	68.21	H%	5.44	Cl%	9.58	N%	3.79
Found:		68.3		5.4		9.6		3.6

Stage C: 1-carboxymethyl-2-methyl-3-(p-chlorobenzoyl)-6-ethylindole

A mixture of 2.2 g 1-(methoxycarbonyl-methyl)-2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole, 1.5 g potassium hydroxide, 100 ml methanol and 10 ml water are refluxed for one hour. The methanol is evaporated off and the residue is dissolved in 100 ml hot water; the solution is treated with carbon and filtered; the filtrate is cooled and brought to pH = 1 by the addition of hydrochloric acid, again filtered, and dried. 2 g of the crude compound are collected (yield 95%); this is recrystallized from methanol. 1.2 g

1-carboxymethyl-2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole are obtained in the form of a solid cream product, soluble in the majority of conventional organic solvents, sparingly soluble in ether and methanol, but insoluble in water, melting at 244°C.

Analysis: $C_{20}H_{18}NClO_3$=355.81

Calculated:	C%	67.55	H%	5.10	Cl%	9.96	N%	3.94
Found:		67.2		5.1		9.7		3.7

Example 2: 1-(1-carboxyethyl)-2-methyl-3-(p-fluorobenzoyl)-6-chloroindole

Stage A: 2-methyl-3-(p-fluorobenzoyl)-6-chloroindole

3.6 g N,N-dimethyl-*p*-fluorobenzamide are dissolved, with agitation, in 1.5 ml phosphorus oxychloride; 3.3 g 2-methyl-6-chloroindole are added, and the reaction mixture is heated at 80—90°C for 2 hours; 100 ml of boiling ethanol are added, and the mixture is poured into hot water with agitation; the solution is cooled, brought to pH=10 by the addition of sodium hydroxide solution, then agitated for 24 hours; the precipitate is filtered and washed with ethanol. 4.2 g 2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole are obtained; this is used as such in the following stage.

The compound appears in the form of a solid yellow product, soluble in dichloromethane, sparingly soluble in alcohols and ether, but insoluble in water, melting at 236°C.

Analysis: $C_{16}H_{10}ClFNO$=286.71

Calculated:	C%	67.03	H%	3.51	Cl%	12.37	F%	6.62	N%	4.89
Found:		67.0		3.9		12.3		6.6		5.0

The starting material, 2-methyl-6-chloroindole, is obtained according to the process described in British Patent No. 1,260,868.

Stage B: Methyl 2-[2-methyl-3-(p-fluorobenzoyl)-6-chloroindol-1-yl]-propionate ester

6.8 g of 2-methyl-3-(p-fluorobenzoyl)-6-chloroindole, 20ml of dimethyl formamide and 1.2 g of a 50% sodium hydride suspension in oil, are mixed with stirring. When the hydrogen has been completely driven off, the mixture is agitated for one more hour, the 4 ml of methyl 2-bromopropionate are added. The mixture is agitated for one night at ambient temperature, the solvent evaporated and the residue taken up in 100 ml water. The mixture is extracted with dichloromethane, the extracts treated with carbon and evaporated to dryness. 3 g of methyl 2-[2-methyl-3-(p-fluorobenzoyl)-6-chloroindol-1-yl] propionate ester are obtained which are used as such in the following stage.

This product occurs in the form of an amorphous compound, soluble in the majority of conventional organic solvents, sparingly soluble in ethanol but insoluble in water.

Stage C: 1-(1-carboxyethyl)-2-methyl-3-(p-fluorobenzoyl)-6 chloroindole

9 g of crude methyl 2-[2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindol-1-yl]-propionate ester, obtained as described above, are refluxed for 1 hour with 2.5 g potassium hydroxide, 200 ml methanol and 10 ml water. The methanol is evaporated off and the dry residue is taken up in 200 ml water; the aqueous solution is treated with carbon and filtered; the filtrate is brought to pH=1 by the addition of hydrochloric acid, filtered, and dried *in vacuo*. 7 g of the residue are recrystallized from a 1:1 water-alcohol mixture and the precipitate is washed with ethanol and then ether and dried. 3.2 g 1-(1-carboxyethyl)-2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole are obtained. melting at 140°C.

Analysis: $C_{19}H_{15}Cl\,FNO_3$=359.78.

Calculated:	C%	63.46	H%	4.2	Cl%	9.85	F.	5.23	N%	3.89
Found:		63.6		4.3		10.1		5.5		4.0

Pharmacological study of 1-carboxymethyl-2-methyl-3-(p-chlorobenzoyl)-6-ethylindole and 1-(1-carboxyethyl)-2-methyl-3-(p-fluorobenzoyl)-6-chloroindole

1) Anti-inflammatory action

The test used is that of D. Branceri, G. Azadian-Boulanger and R. Jequier, slightly modified [*Arch. int. Pharmacodyn., 152*, 15 (1954)]. It comprises administering to rats each weighing about 150 g, in a single injection, 1 mg of naphthoylhepar-

amine (NHA) under the plantar aponeurosis of a rear paw, this injection serving to cause an inflammatory oedema.

The product to be studied is administered orally, in aqueous suspension, one hour before the irritating injection. The inflammation is determined by plethysmometry using an electrical plethysmometer, the volume of the paw being measured immediately before, and two hours after, the irritating injection. The increase in the volume of the paw between these two measurements represents the degree of inflammation. The average degree of inflammation of each group is expressed in absolute quantities and as a percentage of that of control animals. Under these conditions, the standard effective dose which most adequately indicates quantitatively, the activity of a product is the ED_{40}, i.e. the dose which decreases the degree of inflammation by 40% compared with that of the controls.

1. 1-(carboxymethyl)-2-methyl-3-(*p*-chlorobenzoyl)-6-ethyl-indole was administered in doses increasing from 5 to 100 mg/kg.

2. 1-(1-carboxyethyl)-2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole was administered in doses increasing from 5 to 30 mg/kg.

The results obtained are given in the following table:

Batches	Doses administered (mg/kg)	Increase in paw volume after 2 hours	Degree of inflammation as percentage of that of controls
1st test			
Controls	0	15.3	—
1-carboxymethyl-2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole	25	5.8	37
	100	3.6	24
2nd test			
Controls	0	20.3	—
1-carboxymethyl-2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole	5	10.9	54
	15	13.0	64
	45	6.4	31

Batches	Doses administered (mg/kg)	Increase in paw volume after 2 hours	Degree of inflammation as percentage of that of controls
1st test			
Controls	0	14.5	—
1-(1-carboxyethyl) -2-methyl-3-(*p*-fluorobenzoyl)- 6-chloroindole	5	7.0	48
	15	8.6	59
2nd test			
Controls	0	18.6	—
1-(1-carboxyethyl) -2-methyl-3-(*p*-fluorobenzoyl)- 6-chloroindole	3	13.4	72
	9	6.1	33

On the basis of these results it can be seen that the products studied have significant anti-inflammatory activity. For the first product studied, the ED_{40} is below 15 mg/kg, and for the second product studied it is about 5 mg/kg. Under similar experimental conditions the ED_{40} of aspirin is 30—60 mg/kg.

2) Analgesic effect

The test used is based on the observation by R. Koster *et al.* [*Fed. Proc., 18,* 412 (1959)], that the intraperitoneal injection of acetic acid causes, in the mouse, characteristic repeated twisting and stretching movements which can last more than 6 hours. Analgesics prevent or remove this syndrome, which can therefore be considered as the manifestation of a diffuse abdominal pain.

A 0.6% aqueous acetic acid solution, to which 10% of gum Arabic has been added, is used. The dose which initiates the syndrome under these conditions is 0.01 ml/g, i.e. 60 mg/kg, of acetic acid. The analgesics are administered orally in an aqueous solution half an hour before the intraperitoneal injection of acetic acid, the mice having been fasted since the day prior to the experiment. For each dose and for the controls which are compulsory in each test, one more groups of 5 animals are used. The stretching movements of each mouse are observed and counted, then summed by groups of 5 during an observation period of 15 minutes, starting from the moment of injection of acetic acid.

In the case of 1-(1-carboxyethyl)-2-methyl-3-(*p*-fluorobenzoyl)-6-chlorindole, the compound was administered in doses of 2, 5, 10, 20, 50, and 100 mg/kg.

The following table gives the results obtained:

Product	Doses (mg/gk)	Stretching movements as a percentage of the controls
1-carboxymethyl-2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole	5	93
	10	61
	20	28
	50	23
1-(1-carboxyethyl)-2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole	2	96
	5	76
	10	51
	20	24
	50	23
	100	16

These results show that the ED_{50} of the first product studied is about 15 mg/kg, and that of the second product studied is about 10 mg/kg. Under similar conditions, the ED_{50} of aspirin is 160 mg/kg.

3) Research into possible ulcerogenic activity

The ulcerogenic activity was determined by a test devised by Boissier *et al.*, *Therapie*, *22*, 157 (1967).

Female rats each weighing 120—140 g are fasted for 24 hours before the start of the experiment. The products to be studied are administered in aqueous suspension by oral route at a volume of 0.4 ml per 100 g weight of animal, and at increasing doses. The animals are killed 7 hours after the treatment (31 hours after the start of fasting) and the stomachs are removed. The size of the ulcerous lesions is estimated for each stomach, taking account of their number and their dimensions, according to an arbitrary scale from 0~3.

The following results are obtained:

Batches	Dose (mg/kg)	Value from 0 to 3
Controls	0	0
1-carboxymethyl-2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole	200	0.3

Batches	Dose (mg/kg)	Value from 0 to 3
Controls	0	0
1-(1-carboxyethyl)-2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole	20	0.38
	60	1.13

Thus the first compound studied shows no ulcerogenic activity at the high dose of 200 mg/kg.

Under the same experimental conditions, indomethacine causes medium ulcerations (value shown as 1), at doses of 10 mg/kg.

Additional tests on 1-(1-carboxyethyl)-2-methyl-3-(p-fluorobenzoyl)-6-chloroindole

4) Arthritis test using an adjuvant

Injection of the complete Freund adjuvant (*mycobacteria* and mineral oil) into the rear paw of a rat causes:

1. Rapid appearance of a large inflammatory lesion of the injected paw which is called the primary lesion (or arthritis).

2. The appearance, after a latency time of about 15 days, of an inflammatory lesion in the non-injected rear paw and sometimes also the front paws and tail; these lesions are called " secondary arthritis ".

Male rats each weighing 130—150 g are injected via the intraplantar route with 0.1 ml of sterilised adjuvant, " formula No. 4 " (*M. butyricum* 6 mg/ml in Bayol 55: vaseline oil). Starting from the moment of injection (day 0), the animals receive the product studied incorporated in their diet for 17 days (the controls receive the adjuvant only).

The animals are weighed on the day of injection and again after 10 and 17 days. After 8 days and until 17 days have elapsed, an aqueous solution of 1 g/l of tetracycline hydrochloride is administered orally. After 17 days the volume of the non-injected paw is measured by means of a plethysmometer and the serous 2M α-glycoprotein is estimated (this glycoprotein is absent in the normal adult rat but appears in certain pathological conditions such as inflammation).

The results obtained are given in the following table:

Batches	Doses (mg/kg)	Volume of the non-injected paw on day 17	Quantity of 2M α-glycoprotein
Controls	0	63.8	8.20
Studied product	30	31.3	4.66
Controls	0	53.0	6.08
Studied product	1	47.4	4.91
	5	37.2	2.58

These results show that the studied product has a significant anti-inflammatory activity at a dose of 5 mg/kg and that, at this dose, it decreases the serous α 2M glycoprotein level by about 55%.

5) Erythema test using ultra-violet rays

This test is performed on guinea-pigs each weighing 600—900 g according to either of the methods of Winder [*Arch. Int. Pharmacodyn. 116,* 261 (1958)] and Adams [*J. Pharm. Pharmacol., 12,* 251 (1960)]. The product is administered to the animals orally in aqueous suspension one hour before the animals are exposed to ultra-violet rays.

Irradiation takes place for 2 minutes, at a distance of 20 cm on three previously depilated skin areas and the erythema level, evaluated 2 hours after this irradiation, is indicated on an arbitrary scale of magnitude between 0 and 3.

The erythema level of the treated animals is expressed as a percentage of that of the controls which are subjected to the irradiation after receiving only the dispersing agent.

The 1-(1-carboxyethyl)-2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole was administered orally in doses of 20 and 60 mg/kg.

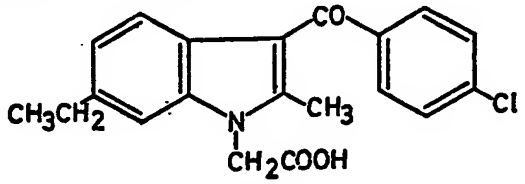
The results obtained are given in the following table:

Batches	Administered doses (mg/kg)	Erythema level (0—3)	Erythema percentage compared with controls)
Controls	0	2.30	100
Product studied	20	1.80	78
Controls	0	2.70	100
Product studied	60	0.70	26

These results show that the dose which decreases inflammation by 50% (ED_{50}) is about 35 mg/kg. Under the same conditions the ED_{50} of aspirin is between 50 and 100 mg/kg.

WHAT WE CLAIM IS:—

1. The compound of formula

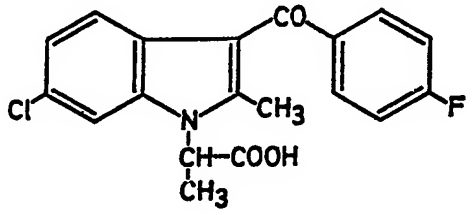


(II)

and physiologically acceptable base salts and esters thereof.

2. The methyl ester of the compound of formula II as defined in claim 1.

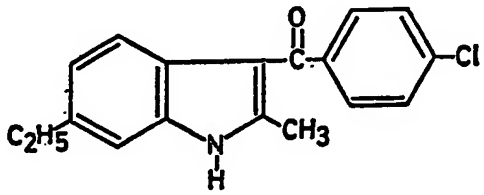
3. The compound of formula



(III)

4. Physiologically acceptable base salts and esters of the compound defined in claim 3.

5. A process for the preparation of the compound of formula II (as defined in claim 1) and C_{1-5} alkyl esters thereof which comprises converting 2-methyl-3-(*p*-chlorobenzoyl)-6-ethylindole, of formula

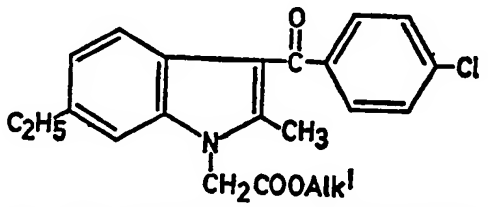


(IV)

to an alkali metal derivative thereof and reacting said derivative with an alkyl haloacetate of formula

$$Hal—CH_2—COOAlk'$$

(wherein Hal represents a chlorine, bromine or an iodine atom and Alk' represents an alkyl group containing 1—4 carbon atoms) to produce a compound of formula



(V)

(wherein Alk' is as defined above) and if desired hydrolysing the last-mentioned compound to the corresponding acid.

6. A process as claimed in claim 5 wherein conversion of the compound of formula IV to its alkali metal derivative is carried out by reaction with an alkali metal amide, alkali metal hydride, an alkali metal alcoholate or a suitable alkali metal organometallic compound.

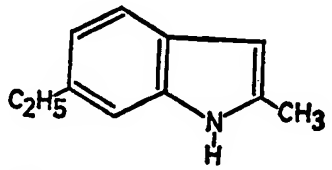
7. A process as claimed in claim 5 or claim 6 wherein the conversion of the compound of formula IV to its alkali metal derivative is effected in an organic solvent.

8. A process as claimed in claim 7 wherein the organic solvent is dimethyl formamide.

9. A process as claimed in any of claims 5—8 wherein hydrolysis of the esters of formula V is carried out under basic conditions in the presence of an organic solvent.

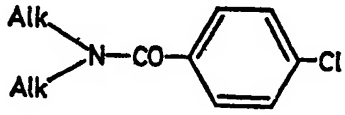
10. A process as claimed in claim 9 wherein the organic solvent, as defined in claim 9, comprises an alkanol.

11. A process as claimed in any of claims 5—10 wherein the compound of formula IV (as defined in claim 5) is prepared by acylating 2-methyl-6-ethylindole of formula



(VI)

with a compound of formula



(VII)

(wherein the groups Alk, which may be the same or different, each represent an alkyl group) and subsequently hydrolysing the complex resulting from the reaction under basic conditions to produce the compound of formula IV.

12. A process as claimed in claim 11 wherein the acylation is effected in the presence of phosphorus oxychloride, phosgene, or thionyl chloride.

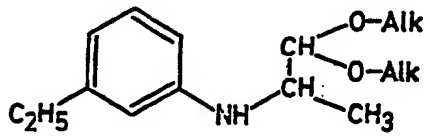
13. A process as claimed in either of claims 11 and 12 wherein the hydrolysis is carried out in the presence of a strong inorganic base.

14. A process s claimed in claim 13 wherein the strong inorganic base is sodium or potassium hydroxide.

15. A process as claimed in any of claims 11 to 14 wherein the hydrolysis is effected in the presence of an organic solvent.

16. A process as claimed in claim 15 wherein the organic solvent comprises an alkanol.

17. A process as claimed in any of claims 11 to 16 wherein the compound of formula VI (as defined in claim 11) is prepared by cyclising a compound of formula

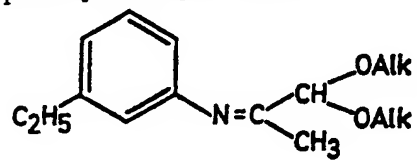


(VIII)

(wherein Alk is as defined in claim 11) with a cyclization agent to produce the compound of formula VI.

18. A process as claimed in claim 17 wherein the cyclization agent is boron trifluoride.

19. A process as claimed in claim 17 or claim 18 wherein the compound of formula VIII is prepared by reducing a compound of formula



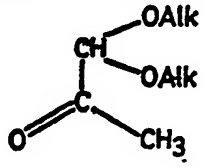
(IX)

(wherein Alk is as defined in claim 11).

20. A process as claimed in claim 19 wherein the reduction of the compound of formula IX is effected with an alkali metal borohydride.

21. A process as claimed in claim 19 wherein the reduction of the compound of formula IX is effected with sodium borohydride.

22. A process as claimed in any of claims 19 to 21 wherein the compound of formula IX is prepared by reacting a compound of formula



(wherein Alk is as defined in claim 11) with 3-ethylaniline.

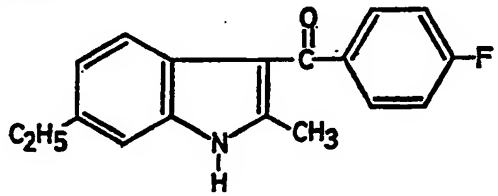
23. A process for the preparation of esters of the compound of formula II (as defined in claim 1) wherein the said compound of formula II is esterified to produce the desired ester.

24. A process as claimed in claim 23 wherein esterification is effected by reacting the compound of formula II with an appropriate alcohol in the presence of an acid catalyst.

25. A process for the preparation of salts of the compound of formula II (as defined in claim 1) wherein the said compound of formula II is converted into the desired salt.

26. A process as claimed in claim 25 wherein the conversion is effected by reacting the compound of formula II with the appropriate base.

27. A process for the preparation of the compound of formula III (as defined in claim 3) and C_{1-8} alkyl esters thereof which comprises converting 2-methyl-3-(*p*-fluorobenzoyl)-6-ethylindole, of formula

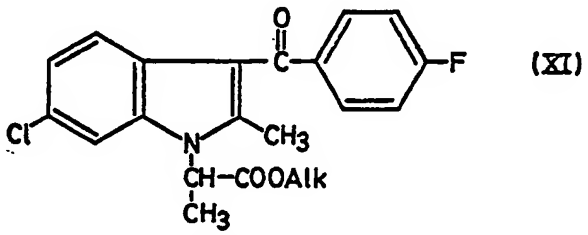


(X)

to an alkali metal derivative thereof and reacting said derivative with an alkyl 2-halopropionate of formula

$$CH_3—CHHal'—COOAlk$$

(wherein Hal' represents a halogen atom and Alk is as defined in claim 11) to produce a compound of formula



(XI)

and if desired hydrolysing the last-mentioned compound to the corresponding free acid.

28. A process as claimed in claim 27 wherein the 2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole is prepared by acylating 2-methyl-6-chloroindole with N,N-dimethyl-*p*-fluorobenzamide and subsequently hydrolysing the resulting complex under basic conditions to produce 2-methyl-3-(*p*-fluorobenzoyl)-6-chloroindole.

29. A process as claimed in claim 28 wherein the acylation is effected in the presence of phosphorus oxychloride, thionyl chloride, or phosgene.

30. A process as claimed in claim 28 or claim 29 wherein the said hydrolysis is effected under the conditions defined in any of claims 11 to 16.

31. A process for preparing the compound of formula II and salts and esters thereof (as defined in claim 1) substantially as herein described.

32. A process for preparing the compound of formula II and salts and esters thereof (as defined in claim 1) substantially as herein described with reference to Example 1.

33. A process for preparing the compound of formula III (as defined in claim 3) substantially as herein described.

34. A process for preparing the compound of formula III (as defined in claim 3) substantially as herein described with reference to Example 2.

35. The compound of formula II and salts and esters thereof (as defined in claim 1) wherever prepared by a process as claimed in any of claims 5—26, 31 or 32.

36. The compound of formula II (as defined in claim 3) whenever prepared by a process as claimed in any of claims 27—30, 33 or 34.

37. Pharmaceutical compositions comprising, as active ingredient, the compound of formula II (as defined in claim 1) and/or a physiologically acceptable base salt or esters thereof, together with at least one pharmaceutical carrier or excipient.

38. Pharmaceutical compositions comprising as active ingredient, the compound of formula III (as defined in claim 3) together with at least one pharmaceutical carrier or excipient.

39. Compositions as claimed in claim 37 or claim 38 presented in a form suitable for oral, transcutaneous, rectal, or topical administration.

40. Compositions as claimed in any of claims 37 to 39 in the form of injectable solutions, injectable suspensions, tablets, coated tablets, capsules, suppositories, ointments, creams or powders for topical application.

41. Compositions as claimed in claim 37 substantially as herein described.

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